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NOTICE OF ALLOWANCE AND FEE(S) DUE

32793 7590 03/18/2009

TAKEDA SAN DIEGO, INC.
10410 SCIENCE CENTER DRIVE
SAN DIEGO, CA 92121

EXAMINER

KIM, ALEXANDER D

ART UNIT

PAPER NUMBER

1656

DATE MAILED: 03/18/2009

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
|-----------------|-------------|----------------------|---------------------|------------------|

10/651,668

08/28/2003

Alexei Brooun

ISPA-5001-C1

9129

TITLE OF INVENTION: CRYSTALLIZATION OF ISPA

| APPLN. TYPE | SMALL ENTITY | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|-------------|--------------|---------------|---------------------|----------------------|------------------|----------|
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nonprovisional

YES

\$755

\$0

\$0

\$755

06/18/2009

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

**Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
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INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

32793 7590 03/18/2009

TAKEDA SAN DIEGO, INC.
10410 SCIENCE CENTER DRIVE
SAN DIEGO, CA 92121

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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

| |
|--------------------|
| (Depositor's name) |
| (Signature) |
| (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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10/651,668 08/28/2003 Alexei Brooun ISPA-5001-C1 9129

TITLE OF INVENTION: CRYSTALLIZATION OF ISPA

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|-------------|--------------|---------------|---------------------|----------------------|------------------|----------|
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nonprovisional YES \$755 \$0 \$0 \$755 06/18/2009

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|----------|----------|----------------|
|----------|----------|----------------|

KIM, ALEXANDER D 1656 702-019000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

- (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, 1 _____
- (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2 _____
- 3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☐ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s); (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27. ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

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Date _____

Typed or printed name _____

Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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|-----------------------------------------------------------------------------|-------------|----------------------|---------------------|------------------|
| 10/651,668 | 08/28/2003 | Alexei Brooun | ISPA-5001-C1 | 9129 |
| 32793 | 7590 | 03/18/2009 | EXAMINER | |
| TAKEDA SAN DIEGO, INC. 10410 SCIENCE CENTER DRIVE SAN DIEGO, CA 92121 | | | KIM, ALEXANDER D | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1656 | |
| DATE MAILED: 03/18/2009 | | | | |

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 439 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 439 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

| | | | |
|-------------------------------|------------------------|---------------------|--|
| Notice of Allowability | Application No. | Applicant(s) | |
| | 10/651,668 | BROOUN ET AL. | |
| | Examiner | Art Unit | |
| | ALEXANDER D. KIM | 1656 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to the amendment filed on 01/02/2009.
2. ☒ The allowed claim(s) is/are 1,4,6,9,18,19 and 21-24.
3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) ☐ All b) ☐ Some* c) ☐ None of the:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
 - * Certified copies not received: ____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
 - (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
 - 1) ☐ hereto or 2) ☐ to Paper No./Mail Date ____.
 - (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date ____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ol style="list-style-type: none"> 1. <input type="checkbox"/> Notice of References Cited (PTO-892) 2. <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) 3. <input type="checkbox"/> Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date ____ 4. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit of Biological Material | <ol style="list-style-type: none"> 5. <input type="checkbox"/> Notice of Informal Patent Application 6. <input type="checkbox"/> Interview Summary (PTO-413), Paper No./Mail Date ____. 7. <input checked="" type="checkbox"/> Examiner's Amendment/Comment 8. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance 9. <input type="checkbox"/> Other ____. |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

DETAILED ACTION

Application Status

1. In response to the previous Office action, a Final rejection (mailed on 10/02/2008), Applicants filed a response and amendment received on 01/02/2009.

Said amendment amended Claims 1 and 6; canceled Claims 2-3, 5, 7-8, 10-17 and 20.

Claims 1, 4, 6, 9, 18-19, 21-24 are pending.

The previous restriction requirement between the inventions of Groups I and II as set forth in the Office action mailed on 3/31/06 is withdrawn by virtue of method Claims 18 and 21-23 being rejoined in accordance with the provisions of MPEP § 821.04. In view of the withdrawal of the restriction requirement as set forth above, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Examiner's amendment to the Claims

2. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided

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by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment shown below was given in a telephone interview with Tao Huang on 13 March 2009.

Amend the claim listing filed on 1/02/2009 with the following changes.

1. A composition comprising a protein, isopentyl pyrophosphate and Risedronate complex in co-crystalline form, wherein the protein of the complex consists of residues 1-314 of SEQ ID NO: 1, wherein said protein is in complex with isopentyl pyrophosphate and Risedronate, and wherein the co-crystal has a crystal lattice in a $P4_122$ space group and unit cell dimensions, $\pm 5\%$, of $a=88.80\text{\AA}$ $b=88.80\text{\AA}$ and $c=174.99\text{\AA}$, $\alpha=\beta=\gamma=90^\circ$.
- 2-3. (Canceled)
4. The composition according to claim 1 wherein the co-crystal diffracts X-rays for a determination of structure coordinates to a resolution of a value equal to or less than 3.0\AA .
5. (Canceled)
6. A method for forming a co-crystal of a protein, isopentyl pyrophosphate and Risedronate comprising:
forming a crystallization volume comprising a precipitant solution, isopentyl pyrophosphate, Risedronate and a protein that consists of

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residues 1-314 of SEQ ID NO: 1, wherein said protein is in complex with isopentyl pyrophosphate and Risedronate; and storing the crystallization volume under conditions suitable for formation of a protein, isopentyl pyrophosphate and Risedronate complex co-crystal, wherein the co-crystal has a crystal lattice in a $P4_122$ space group and unit cell dimensions, $\pm 5\%$, of $a=88.80\text{\AA}$, $b=88.80\text{\AA}$ and $c=174.99\text{\AA}$, $\alpha=\beta=\gamma=90^\circ$.

7-8. (Canceled)

9. The method according to claim 6 wherein the co-crystal diffracts X-rays for a determination of structure coordinates to a resolution of a value equal to or less than 3.0\AA .

10-17. (Canceled)

18. A method of solving a structure of a protein comprising:

forming a crystallization volume comprising a precipitant solution, isopentyl pyrophosphate, Risedronate and a protein that consists of residues 1-314 of SEQ ID NO: 1, wherein said protein is in complex with isopentyl pyrophosphate and Risedronate; storing the crystallization volume under conditions suitable for formation of a protein, isopentyl pyrophosphate and Risedronate complex co-crystal, wherein the co-crystal has a crystal lattice in a $P4_122$ space group and unit cell dimensions, $\pm 5\%$, of $a=88.80\text{\AA}$, $b=88.80\text{\AA}$ and $c=174.99\text{\AA}$, $\alpha=\beta=\gamma=90^\circ$; diffracting the co-crystal to produce a diffraction pattern; and solving the structure of the protein from the diffraction pattern.

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19. A non-crystalline protein consisting of residues 1-314 of SEQ ID NO: 1.
20. (Canceled)
21. A method of identifying an entity that potentially associates with a protein comprising:
 - forming a crystallization volume comprising a precipitant solution, isopentyl pyrophosphate, Risedronate and a protein that consists of residues 1-314 of SEQ ID NO: 1, wherein said protein is in complex with isopentyl pyrophosphate and Risedronate;
 - storing the crystallization volume under conditions suitable for formation of a protein, isopentyl pyrophosphate and Risedronate complex co-crystal, wherein the co-crystal has a crystal lattice in a $P4_122$ space group and unit cell dimensions, $\pm 5\%$, of $a=88.80\text{\AA}$ $b=88.80\text{\AA}$ and $c=174.99\text{\AA}$, $\alpha=\beta=\gamma=90^\circ$;
 - diffracting the co-crystal to produce a diffraction pattern;
 - solving the structure of the protein from the diffraction pattern;
 - performing rational drug design using the solved structure; and
 - identifying an entity that associates with the protein.
22. The method according to claim 21 further comprising selecting one or more entities based on the rational drug design and contacting the selected entities with the protein.
23. The method according to claim 22 further comprising measuring an activity of the protein when contacted with the one or more entities.
24. An isolated non-crystalline protein consisting of residues 1-314 of SEQ ID NO: 1.

Statement of Reasons for Allowance

3. Claims 1, 4, 6, 9, 18-19, and 21-24 are allowed. The following is an examiner's statement of reasons for allowance:

The instant invention is drawn to a composition comprising a protein, isopentyl pyrophosphate and Risedronate complex in co-crystalline form wherein the protein is 1-314 of SEQ ID NO: 1 (i.e., farnesyl pyrophosphate synthase); a method of forming said co-crystal; a method of solving a structure of said co-crystal; and a method of identifying an entity that potentially associates with the protein of 1-314 of SEQ ID NO: 1.

According to the specification, human farnesyl pyrophosphate synthase is the molecular target of the N-containing bisphosphonate drugs used to treat osteoporosis (p. 12, paragraph 44). The claimed co-crystal having the recited space group and unit cell dimensions is novel and not obvious. The co-crystal is useful for providing three dimensional structural information and can be used to design a compound capable of binding to the farnesyl pyrophosphate synthase based on the three dimensional structure of the co-crystal through X-ray crystallography.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEXANDER D. KIM whose telephone number is (571)272-5266. The examiner can normally be reached on 11AM-7:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alexander D Kim/
Examiner, Art Unit 1656

/David J. Steadman/
Primary Examiner, Art Unit 1656